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Therapeutic Class Review
Proton-Pump Inhibitors - Single Entity Agents

Overview/Summary

Proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally recognized as the most potent acid suppressants available.[1] Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase (H^+K^+-exchanging ATPase) is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K+) for hydrogen ions (H+) resulting in a lower gastric pH. PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. PPIs will only inhibit proton pumps that are actively secreting acid.[1] Following a meal approximately 70%-80% of the proton pumps will be active.[2] Thus single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in 3-4 days.[1-3]

Currently, there are 5 PPIs available on the market in a variety of formulations, including one over-the-counter product (Prilosec OTC®). The PPIs are esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole, of which omeprazole and pantoprazole are available generically. All 5 PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole represents a formulation that contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. Primary differences between the PPIs occur in their pharmacokinetic and pharmacodynamic properties along with formulation availability. Numerous studies have compared the various PPIs to one another. While some differences have been reported, the magnitude of these differences has been small and of questionable clinical significance.[3] In general, when given in equivalent dosages, the PPIs have shown comparable efficacy.

Clinical studies have demonstrated that PPIs are effective for treatment of all acid-related disorders.[3] National and international consensus guidelines recognize PPIs as first-line therapy for the management of dyspepsia, gastroesophageal reflux disease (GERD), peptic ulcer disease and eradication of *Helicobacter pylori.*[17-23] The guidelines do not give preference to one PPI over another.

Medications

Table 1. Medications Included Within Class Review[4-16]

Generic Name (Trade name)	Medication Class	Generic Availability
Esomeprazole (Nexium®, Nexium IV®)	Proton-pump inhibitors	-
Lansoprazole (Prevacid®, Prevacid IV®, Prevacid SoluTab®)	Proton-pump inhibitors	-
Omeprazole (Prilosec®)	Proton-pump inhibitors	✔
Omeprazole magnesium (Prilosec OTC®)	Proton-pump inhibitors	✔
Omeprazole and sodium bicarbonate (Zegerid®)	Proton-pump inhibitors	-
Pantoprazole (Protonix®, Protonix IV®)	Proton-pump inhibitors	✔
Rabeprazole (Aciphex®)	Proton-pump inhibitors	-

Indications

Table 2. Food and Drug Administration-Approved Indications[4-16]

Indication	Esomep-razole	Lansop-razole	Omep-razole	Pantop-razole	Rabep-razole
Gastroesophageal Reflux Disease (GERD)					
Treatment of erosive esophagitis (short term)	✔ *†	✔ *†	✔ †	✔	✔
Maintenance of healing of erosive esophagitis	✔	✔	✔ †	✔	✔
Treatment of symptomatic GERD	✔ †	✔ †	✔ †	✔ §	✔ †
Peptic Ulcer Disease (PUD)					
Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence	✔ ‡	✔ ‡	✔ ‡ (Prilosec®)		✔ ‡
Treatment of active duodenal ulcers (short term)		✔	✔		✔
Maintenance of healed duodenal ulcers		✔			
Treatment of active, benign gastric ulcer (short term)		✔	✔		
Healing of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer		✔			
Risk reduction of NSAID-associated gastric ulcer	✔	✔			
Other					
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome (long term)	✔	✔	✔ (Prilosec®)	✔ *	✔
Risk reduction of upper gastrointestinal bleeding in critically ill patients			✔ (Zegerid®)		
Treatment of frequent heartburn for up to 14 days			✔ (Prilosec OTC®)		

*Oral and intravenous formulation.
†Adult and pediatric patients.
‡As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole, lansoprazole, omeprazole and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).
§Intravenous formulation indicated for treatment of GERD associated with a history of erosive esophagitis.

Pharmacokinetics

As noted in Table 3, there are some differences in the pharmacokinetic properties of the proton-pump inhibitors (PPIs), particularly with regards to bioavailability and metabolism. While they are all hepatically metabolized, the PPIs are metabolized by different pathways within the cytochrome P450 (CYP) enzyme system. The relative importance of the CYP2C19 pathway on the metabolism of PPIs has been reported to be omeprazole = esomeprazole > pantoprazole > lansoprazole > rabeprazole.[24] Depending upon their CYP2C19 genotype, patients may be considered extensive, intermediate or poor metabolizers. Approximately 67% of Caucasians are extensive metabolizers and about 5% are slow metabolizers.[3] A few studies have reported higher cure rates for gastroesophageal reflux disease (GERD) and eradication of *H pylori* in patients who were poor metabolizers.[3,24] Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.

Table 3. Pharmacokinetics[3-16]

Generic Name	Bioavailability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (hours)
Esomeprazole	64 (single dose) ~90 (multiple	1.5	~80	CYP2C19, CYP3A4 (none)	1-1.5

Generic Name	Bioavailability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (hours)
	doses)				
Lansoprazole	>80	1.7	14-25	CYP2C19, CYP3A4 (cyclic sulfenamide and disulfide metabolites)	0.9-1.5
Omeprazole	30-40	0.5-3.5	77	CYP2C19 (none)	0.5-1
Omeprazole magnesium	Not reported	Not reported	Not reported	CYP2C19 (none)	0.5-1
Omeprazole and sodium bicarbonate	30-40	0.5	77	CYP2C19 (none)	0.5-1
Pantoprazole	77	2.5	71	CYP2C19, CYP3A4 (not reported)	1
Rabeprazole	~52	2.0-5.0	90	CYP2C19, CYP3A4 (not reported)	1-2

Clinical Trials

Clinical trials have demonstrated that proton-pump inhibitors (PPIs) are highly effective in treating, providing symptomatic relief and preventing relapse in gastric acid disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease.[25-66] There is an abundance of data comparing the efficacy and safety of the individual PPIs for the treatment and/or management of these disorders. In meta-analyses and direct comparator trials, lansoprazole, omeprazole, pantoprazole and rabeprazole all demonstrated comparable healing rates, maintenance of healing, or symptomatic relief of GERD.[25-27,45,48-50] Richter et al reported that lansoprazole produced a statistically quicker and greater symptomatic relief of GERD than omeprazole; however, the absolute differences in this study were small and the clinical impact of the difference was not measured within the trial.[46]

There is evidence through meta-analyses and several clinical trials that esomeprazole provides higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole at 4 and 8 weeks.[25,27,29,31,32,35,37,40,41] Subgroup analyses in a few trials noted better healing rates with esomeprazole in patients with more severe disease.[38,40] Close analyses of all of these studies show that the overall differences were generally small. Though the results are statistically significant, the clinical significance of these differences is not clear. In addition, the results of these trials have not been replicated consistently in other trials, particularly in trials with lansoprazole and pantoprazole.[28,30,36,39,42,44] It should be noted that most trials comparing esomeprazole to omeprazole utilized a dose of 40 mg for esomeprazole and 20 mg for omeprazole.[25,27,35,37] Since esomeprazole is a stereoisomer of omeprazole, comparing 40 mg of esomeprazole to 20 mg of omeprazole is comparable to evaluating a double dose of omeprazole.[25] Lightdale et al reported comparable healing rates and symptom relief in patients with erosive esophagitis treated with 20 mg daily of esomeprazole or omeprazole.[39] A 2007 Cochrane review concluded that there was no major difference in efficacy among the currently available PPs for the short-term management of reflux esophagitis when administered in equivalent dosages.[51]

Meta-analyses and head-to-head trials comparing PPPIs for the treatment of peptic ulcer disease with *H pylori* have shown comparable rates of eradication when paired with comparable antibiotic regimens.[52-56,58-61] One small trial reported higher eradication rates for patients treated with esomeprazole than pantoprazole.[57]

Stable Therapy

Nelson et al conducted an analysis of the impact of converting patients with GERD from omeprazole to lansoprazole through a managed care plan policy change.[67] Patients converted were surveyed by telephone prior to the interchange and 30 days after the interchange. One hundred and five patients

completed both interviews. After the interchange, increased frequency of heartburn while awake was reported in 37% of the patients, 9% reported increased frequency of heartburn that kept them from falling asleep, 33% reported increased frequency of use of any over-the-counter (OTC) heartburn preparations, and 13% reported increased frequency of diet change due to heartburn symptoms (*P* values not reported). Mean patient satisfaction scores based on a 10-point scale (1 being not satisfied and 10 being completely satisfied) decreased significantly from baseline (9.0 vs 7.2; *P*<0.001).

Cote et al evaluated whether patients with GERD who were previously managed on lansoprazole 30 mg twice daily could be maintained on rabeprazole 20 mg once daily after a formulary change at a Veterans' Affairs hospital.[68] Of 435 patients who had received lansoprazole 30 mg twice daily for at least 12 months, data was evaluated for 223 patients. Of these patients, 111 (50%) were successfully maintained on rabeprazole 20 mg once daily, 23 (10%) were able to discontinue PPI therapy and 89 (40%) were considered treatment failures (subsequent increase in PPI dose or a switch of PPI). Of these, 82 patients had recurrent GERD symptoms while on rabeprazole 20 mg once daily. (Of note, data for about half of the patients was excluded for reasons such as no documentation of GERD in the medical record, recent diagnosis of peptic ulcer, lack of follow-up, and never received once daily PPI.)

Impact on Physician Visits

Meineche-Schmidt conducted a study in 829 patients investigating the long-term effect of health-care consumption when double doses of omeprazole were utilized.[69] Patients with dyspeptic symptoms were randomized to receive omeprazole 40 mg, omeprazole 20 mg, or placebo every morning for 2 weeks. Patients were evaluated on symptom relief. In addition, relapse rates and health-care consumption after 12 months were recorded. Complete symptom relief was comparable between omeprazole 40 mg (66.4%) and omeprazole 20 mg (63.0%) but higher than placebo (34.9%; no *P* values reported). Relapse rates after 12 months were comparable between all treatment arms (67.7% for omeprazole 40 mg, 64.7% for omeprazole 20 mg and 63.3% for placebo). There was no difference between treatment arms in the number of contacts with the general practitioner, referrals to specialists, hospitals, or use of dyspepsia medications (specific data not reported).

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gastroesophageal Reflux Disease (GERD)				
Klok et al[25] Direct comparison of short-term PPI therapy under the same clinical conditions	MA Randomized trials of PPI use in GERD, PUD, or *H pylori* eradication	41 trials Duration varied	Primary: Success rates (defined as endoscopically determined cure for GERD and PUD or absence of *H pylori*) Secondary: Not reported	Primary: Comparisons between PPI treatment for GERD included the following: esomeprazole 40 mg vs omeprazole 20 mg daily; esomeprazole 20 mg vs omeprazole 20 mg daily; lansoprazole 30 mg daily vs omeprazole 20 mg daily; lansoprazole 30 mg daily vs omeprazole 40 mg daily; lansoprazole 15 mg daily vs omeprazole 20 mg daily; lansoprazole 30 mg daily vs pantoprazole 40 mg daily. pantoprazole 40 mg daily vs omeprazole 20 mg daily; pantoprazole 20 mg daily vs omeprazole 20 mg daily; rabeprazole 20 mg daily vs omeprazole 20 mg daily; and rabeprazole 10 mg daily vs omeprazole 20 mg daily. For GERD treatment, one statistically significant difference was noted. After 4 weeks of treatment, esomeprazole 40 mg per day was found to have significantly greater healing rates compared to omeprazole 20 mg per day (RR, 1.18; 95% CI, 1.14 to 1.23). For all other comparisons in GERD, no significant difference was found. Comparisons between PPI treatment for ulcer healing included the following: esomeprazole 40 mg vs omeprazole 20 mg daily; lansoprazole 30 mg daily vs omeprazole 20 mg daily; pantoprazole 40 mg daily vs omeprazole 20 mg daily; rabeprazole 20 mg daily vs omeprazole 20 mg daily. For PUD treatment, one statistically significant difference was noted. After 4 weeks of treatment, pantoprazole 40 mg/day was found to have significantly greater healing rates compared to omeprazole 20 mg per day (RR, 1.07; 95% CI, 1.02 to 1.13). For all other comparisons, no significant difference was found. No significant differences were found in *H pylori* eradication rates between PPIs.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Caro et al[26] Omeprazole, ranitidine or placebo vs lansoprazole, pantoprazole, or rabeprazole	MA Randomized trials for GERD acute and maintenance therapy (placebo arm included)	41 trials Duration varied	Primary: Healing and relapse rates Secondary: Not reported	Primary: Compared to omeprazole 20 mg daily, the healing rate ratios after 8 weeks were as follows: lansoprazole 30 mg daily, healing rate ratios=1.02 (95% CI, 0.98 to 1.06); rabeprazole 20 mg daily, healing rate ratios=0.93 (95% CI, 0.87 to 1.00); and pantoprazole 40 mg daily, healing rate ratios=0.98 (95% CI, 0.90 to 1.07). Relapse rates after 6 months were as follows: lansoprazole 30 mg daily 6%-29%; rabeprazole 20 mg daily 9%; and omeprazole 20 mg daily 7%-42%. No maintenance trials with pantoprazole were included. Secondary: Not reported
Edwards et al[27] Omeprazole 20 mg daily vs esomeprazole 40 mg daily, lansoprazole 30 mg daily, pantoprazole 40 mg daily, or rabeprazole 20 mg daily	MA Randomized trials comparing omeprazole to other PPIs for acute treatment for GERD	12 trials 4-8 weeks	Primary: Healing rates Secondary: Not reported	Primary; Compared to omeprazole 20 mg daily, esomeprazole 40 mg daily had significantly greater healing rates at week 4 (RR, 1.14; 95% CI, 1.10 to 1.18) and at week 8 (RR, 1.08; 95% CI, 1.05 to 1.10). Compared to omeprazole 20 mg daily, there was no significant difference in healing rates at 4 or 8 weeks with lansoprazole 30 mg daily, pantoprazole 40 mg daily, and rabeprazole 20 mg daily. Secondary: Not reported
Chey et al[28] Esomeprazole 40 mg DAILY vs lansoprazole 30 mg DAILY	DB, MC, RCT Adult patients with symptomatic GERD	N=3,034 2 weeks	Primary: Average symptom severity after day 3 Secondary: Percentage of patients without daytime and	Primary: No statistically significant differences were noted between the two treatment groups in symptom severity after day 3 (*P* value not reported). Secondary: No statistically significant differences were noted for any of the secondary endpoints (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			nighttime heartburn after day 1, symptom relief after day 1, and symptom severity after day 1, day 7, and day 14	
Castell et al[29] Esomeprazole 40 mg DAILY in the morning vs lansoprazole 30 mg DAILY in the morning	DB, MC, PG, RCT Adults with endoscopically documented erosive esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders or strictures, Barrett's esophagitis, upper GI malignancy, or other severe concomitant disease	N=5,241 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at week 4, resolution of investigator-recorded heartburn at week 4, time to first and time to sustained relief of heartburn and proportion of heartburn-free days and nights	Primary: Esomeprazole demonstrated significantly higher healing rates at 8 weeks compared to lansoprazole (92.6% vs 88.8%; *P*=0.0001). Secondary: Esomeprazole demonstrated higher healing rates at 4 weeks compared to lansoprazole (79.4% vs 75.1%; *P* value not reported). Resolution of heartburn at week 4 was significantly higher with esomeprazole compared to lansoprazole (62.9% vs 60.2%; *P*≤0.05). No significant difference was observed in time to first resolution of heartburn (median of 2 days for both treatment groups); however, time to sustained relief was significantly less with esomeprazole (7 vs 8 days; *P*≤0.01). There was no significant difference in the proportion of heartburn-free days between treatment groups; however, heartburn-free nights were significantly higher with esomeprazole (87.1% vs 85.8%; *P*≤0.05).
Howden et al[30] Esomeprazole 40 mg DAILY vs	DB, MC, RCT Adult patients with endoscopically documented erosive esophagitis	N=284 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at week 4,	Primary: Comparable healing rates at week 8 were observed between esomeprazole compared to lansoprazole (89.1% vs 91.4%, respectively; *P* value not reported). Secondary: Healing rates at week 4 were comparable between the two treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lansoprazole 30 mg DAILY			proportion of patients reporting heartburn-free days and nights, and rate of healing or improvement of esophagitis by 2 grades	groups (77.0% for lansoprazole and 78.3% for esomeprazole; *P* value not reported). The percentage of patients reporting heartburn-free days and nights was comparable between treatment groups. Healing or improvement of esophagitis by 2 grades was observed in 90% of patients taking lansoprazole and 81% taking esomeprazole.
Devault et al[31] Esomeprazole 20 mg DAILY vs lansoprazole 15 mg DAILY	DB, MC, PG, RCT Patients 18-75 years with erosive esophagitis (Los Angeles grades A, B, C or D) who were treated and healed Patients excluded if they had other GI complications, bleeding disorders or other diseases or conditions that could affect study participation	N=1,026 6 months	Primary: Remission rates (defined as no detectable erosive esophagitis and no study discontinuation due to reflux symptoms) estimated by Kaplan-Meier at 6 months Secondary: Observed remission rate at 3 months and 6 months	Primary: Estimated endoscopic/symptomatic remission rate during a period of 6 months was significantly higher (*P*=0.0007) for patients on esomeprazole (84.8%) compared to lansoprazole (75.9%). Secondary: Observed endoscopic/symptomatic remission rates at 3 months (92.8% vs 86.8%; *P*<0.0001) and 6 months (86.2% vs 77.6%; *P*<0.0001) were significantly higher in the esomeprazole group compared with the lansoprazole group. There was no significant difference between esomeprazole and lansoprazole at 6 months with regards to patients reporting no heartburn (82.9% and 79.2%), acid regurgitation (86.8% and 85.8%), dysphagia (97.6% and 96.4%) or epigastric pain (91.6% and 89.5%). Both treatments were well tolerated.
Fennerty et al[32] Esomeprazole 40 mg DAILY vs lansoprazole 30 mg DAILY	DB, MC, RCT Patients with moderate-severe erosive esophagitis (Los Angeles Grade C or D) Patients excluded if	N=999 8 weeks	Primary: Healing rates at week 8 Secondary: Resolution of heartburn symptoms at week 4	Primary: Healing rates at week 8 were significantly greater in patients taking esomeprazole compared to lansoprazole (82.4% vs 77.5%; *P*=0.007). Secondary: Significantly more patients taking esomeprazole had resolution of heartburn symptoms at week 4 than lansoprazole (72.0% vs 63.6%; *P*=0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	they had GI bleeding, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, inflammatory bowel disease, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer, upper GI malignancy, or other severe concomitant disease			
Metropole Study[33] Esomeprazole 20 mg DAILY vs lansoprazole 15 mg DAILY	DB, MC, RCT Patients with healed esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, inflammatory bowel disease, esophageal stricture, Barrett's esophagitis, duodenal or gastric	N=1,391 6 months	Primary: Remission rates at 6 months Secondary: Not reported	Primary: Remission rates at 6 months were significantly higher with esomeprazole compared to lansoprazole (83% vs 74%; *P*<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	ulcer, upper GI malignancy, or other severe concomitant disease			
COMMAND Study[34] Esomeprazole 20 mg on-demand therapy (PRN) vs lansoprazole 15 mg DAILY All patients received esomeprazole 20 mg DAILY for 2-4 weeks for acute treatment of GERD, then proceeded into the maintenance phase and were randomized into the above treatment groups.	MC, PG, RCT, SB Patients 18-80 years of age with >6 month history of GERD without esophageal mucosal breaks and reported symptoms in >4 out of the previous 7 days Patients excluded if they received >10 days of PPI therapy in the previous 28 days, were on anticholinergics, cisapride, prostaglandin analogues, NSAIDs, or salicylates	N=622 6 months	Primary: Time to discontinuation from maintenance phase due to unwillingness to continue Secondary: Time to discontinuation due to insufficient heartburn control, patient satisfaction, and symptom assessment	Primary: Time to discontinuation from maintenance phase due to unwillingness to continue was significantly longer for patients taking esomeprazole PRN compared to lansoprazole DAILY (*P*=0.001). At 6 months, significantly more patients on lansoprazole were unwilling to continue therapy compared to esomeprazole (13% vs 6%; *P*=0.001). Secondary: Of the patients that discontinued therapy, 4.8% taking lansoprazole and 2.9% taking esomeprazole reported heartburn as the reason for unwillingness to continue (*P* value not reported). The time to discontinuation due to insufficient heartburn control was not reported. Significantly more patients cited adverse events with lansoprazole as the reason for unwillingness to continue treatment (*P*=0.0028). Patient satisfaction was significantly higher with esomeprazole after 1 month of treatment (*P*=0.02). At 3 and 6 months, patient satisfaction was similar for both groups. The frequency of heartburn symptoms recorded at clinic visits was higher with esomeprazole compared to lansoprazole at 1, 3, and 6 months (*P* value not reported).
Richter et al[35] Esomeprazole 40 mg DAILY vs omeprazole 20 mg DAILY	DB, MC, PG, RCT Adult patients with erosive esophagitis Patients excluded if they tested positive for *H pylori*, had GI bleeding, history of gastric or	N=2,425 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at 4 weeks, and resolution of heartburn symptoms at	Primary: Significantly more patients taking esomeprazole were healed at 8 weeks compared to those taking omeprazole (93.7% vs 84.2%; *P*<0.001). Secondary: Significantly more patients taking esomeprazole were healed at 4 weeks compared to those taking omeprazole (81.7% vs 68.7%; *P*<0.001). Significantly more patients taking esomeprazole had complete resolution of heartburn compared to those taking omeprazole (68.3% vs 58.1%;

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	esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, duodenal or gastric ulcer, inflammatory bowel disease, upper GI malignancy, unstable diabetes or other severe concomitant disease		week 4, time to first resolution and sustained resolution of heartburn, and proportion of heartburn-free days and nights	*P*<0.001). Time to first resolution was significantly greater with esomeprazole at day 1 (45.3% vs 32.0%; *P*≤0.0005) and day 7 (85.6% vs 81.6%; *P*≤0.0005) compared to omeprazole. Time to sustained resolution with esomeprazole was significantly greater at day 1, 14, and 28 compared to omeprazole (*P*≤0.0005). Esomeprazole resulted in greater heartburn-free days (74.9% vs 69.7%) and nights (90.8% vs 87.9%; both *P*<0.001).
Armstrong et al[36] Esomeprazole 40 mg DAILY vs esomeprazole 20 mg DAILY vs omeprazole 20 mg DAILY In study A, patients received either esomeprazole 40 mg DAILY, esomeprazole 20 mg DAILY, or omeprazole 20 mg	3 RCT, DB, MC, PG Patients with heartburn for >6 months with a normal endoscopy were included in one of 3 trials	N=2,645 4 weeks	Primary: Complete resolution of heartburn at 4 weeks Secondary: Complete resolution of heartburn at 14 days, adequate control of heartburn, relief of other reflux and GI symptoms, and relief of heartburn (assessed by patient diary)	Primary: Complete resolution of heartburn at 4 weeks was comparable for all treatment arms throughout the 3 studies. Secondary: Complete resolution of heartburn at 2 weeks was comparable for all treatment arms throughout the 3 studies. For adequate control of heartburn in study A, 60.5% taking esomeprazole 40 mg, 66.0% on esomeprazole 20 mg, and 63.1% on omeprazole 20 mg reported adequate control (*P* value not reported). In study B, 73.5% taking esomeprazole 40 mg and 72.8% on omeprazole 20 mg reported adequate heartburn control (*P* value not reported). In study C, 67.9% taking esomeprazole 20 mg and 65.3% on omeprazole 20 mg reported adequate heartburn control (*P* value not reported). After 4 weeks, relief of other reflux and gastrointestinal symptoms was comparable in all treatment arms throughout the 3 studies.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DAILY. In study B patients received esomeprazole 40 mg DAILY or omeprazole 20 mg DAILY and in study C, patients received esomeprazole 20 mg DAILY or omeprazole 20 mg DAILY				In study A, relief of heartburn reported by patients was higher with esomeprazole 20 mg (*P* value not reported). No differences were detected throughout the other 2 studies.
Kahrilas et al[37] Esomeprazole 40 mg DAILY vs esomeprazole 20 mg DAILY vs omeprazole 20 mg DAILY	DB, MC, PG, RCT Patients with endoscopically documented reflux esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal motility disorders, esophageal stricture, Barrett's esophagitis, upper GI malignancy, or other severe concomitant disease	N=1,960 8 weeks	Primary: Healing rates after 8 weeks Secondary: Resolution of heartburn symptoms at week 4, time to first and time to sustained relief of heartburn, and proportion of heartburn-free days and nights	Primary: Healing rates for both esomeprazole 40 mg DAILY (94.1%; *P*<0.001 vs omeprazole) and 20 mg DAILY (89.9%; *P*<0.05 vs omeprazole) were statistically higher than omeprazole 20 mg DAILY (86.9%). Secondary: Resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg compared to those taking omeprazole 20 mg (64.7% vs 57.2%; *P*=0.005). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (61.0%). Time to first resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg compared to omeprazole (*P*=0.013). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg. Time to sustained resolution of heartburn symptoms was significantly higher for patients taking esomeprazole 40 mg (5 days) compared to omeprazole (9 days; *P*=0.0006). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (8 days). Proportion of heartburn-free days was significantly higher for patients taking esomeprazole 40 mg (72.7%) compared to omeprazole (67.1%; *P*=0.002). There were no significant differences between omeprazole 20 mg and esomeprazole 20 mg (69.3%). Proportion of heartburn-free nights was significantly higher for patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				taking esomeprazole 40 mg (84.7%; *P*=0.001) and 20 mg (83.6%; *P*=0.013) compared to omeprazole (80.1%).
Schmitt et al[38] Esomeprazole 40 mg DAILY vs omeprazole 20 mg DAILY	DB, MC, PG, RCT Patients 18-75 years old with erosive esophagitis confirmed by endoscopy Patients excluded if positive for *H pylori*, any bleeding disorder, history of gastric or esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures, or Barrett's esophagus	N=1,148 8 weeks	Primary: Proportion of patients with healed erosive esophagitis at week 8 Secondary: Diary and investigator assessments of heartburn symptoms, safety	Primary: The proportion of patients with healed erosive esophagitis at week 8 was 92.2% for esomeprazole and 89.9% for omeprazole (*P*=0.189). The proportion of patients with healed erosive esophagitis at week 4 was 71.5% for esomeprazole and 68.6% for omeprazole (no *P* value reported). Healing rates with esomeprazole were significantly higher than those with omeprazole at weeks 8 (88.4% vs 77.5%; *P*=0.007) and 4 (60.8% vs 47.9%; *P*=0.02) in patients with moderate-to-severe (Los Angeles grade C or D) erosive esophagitis at baseline but were not significantly different for patients with mild disease (grade A or B). Secondary: After 4 weeks of treatment, there were no significant differences between esomeprazole and omeprazole in the proportions of patients with investigator-assessed resolution of heartburn (65.0% vs 63.1%; *P*=0.48), the percentage of heartburn-free days (74.5% vs 73.0%; *P*=0.39) or the percentage of heartburn-free nights (86.2% vs 84.5%; *P*=0.21). Both treatments had similar tolerability.
Lightdale et al[39] Esomeprazole 20 mg DAILY vs omeprazole 20 mg DAILY	DB, MC, PG, RCT Patients 18-75 years old with erosive esophagitis confirmed by endoscopy Patients excluded if positive for *H pylori*, any bleeding disorder, history of gastric or	N=1,176 8 weeks	Primary: Proportion of patients with healed erosive esophagitis at weeks 8 Secondary: Diary and investigator assessments of heartburn symptoms, safety	Primary: The proportion of patients with healed erosive esophagitis at week 8 was 90.6% for esomeprazole and 88.3% for omeprazole (*P*=0.621). Similar healing rates were achieved at weeks 4 and 8 with esomeprazole and omeprazole in the entire study population and when patients were classified according to baseline severity of erosive esophagitis. Secondary: Patients in both treatment groups had similar control of heartburn at week 4. Adverse events were reported with similar frequencies among the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	esophageal surgery, Zollinger-Ellison syndrome, esophageal strictures, or Barrett's esophagus			esomeprazole and omeprazole patients.
EXPO Study[40] (Treatment) Esomeprazole 40 mg DAILY vs pantoprazole 40 mg DAILY	DB, MC, RCT Adult patients with erosive esophagitis confirmed by endoscopy Patients were excluded if they had peptic ulcers, Zollinger-Ellison syndrome, esophageal stricture, or Barrett's esophagitis	N=3,170 8 weeks	Primary: Healing rates at 8 weeks Secondary: Healing rates at 4 and 8 weeks by baseline esophagitis severity, time to sustained symptom relief, and proportion of heartburn-free days	Primary: At 8 weeks, healing rates for esomeprazole 40 mg DAILY (95.5%) were statistically higher than for pantoprazole 40 mg DAILY (92.0%; *P*<0.001). Secondary: At 4 and 8 weeks, healing rates for esomeprazole 40 mg DAILY were statistically higher than for pantoprazole 40 mg DAILY for erosive esophagitis grades B-D (Los Angeles grading; *P*<0.05). No significant difference was noted for grade A esophagitis. Time to sustained resolution of heartburn symptoms was significantly shorter with esomeprazole 40 mg (6 days) compared to pantoprazole (8 days; *P*<0.001). Proportion of heartburn-free days was significantly higher with esomeprazole 40 mg (70.7%) compared to omeprazole (67.3%; *P*<0.01).
EXPO Study[41] (Maintenance) Esomeprazole 20 mg DAILY vs pantoprazole 20 mg DAILY	DB, MC, RCT Patients from the EXPO Study with healed erosive esophagitis (confirmed by endoscopy at weeks 4 or 8) and free of moderate-to-severe heartburn and acid regurgitation for 7 days prior to the maintenance study	N=2,766 6 months	Primary: Proportion of patients in endoscopic plus symptomatic remission Secondary: Relapse based on endoscopic findings	Primary: Following 6 months of treatment, the proportion of patients in endoscopic and symptomatic remission was significantly greater for those receiving esomeprazole 20 mg (87.0%) than pantoprazole 20 mg (74.9%; *P*<0.0001). Post hoc analyses showed that esomeprazole was significantly more effective than pantoprazole in patients with Los Angeles grades A, B and C but not grade D. Esomeprazole 20 mg produced a higher proportion of patients free of moderate-to-severe gastroesophageal reflux disease symptoms and fewer discontinuations because of symptoms than pantoprazole 20 mg (92.2% vs 88.5%; *P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	entry (see above EXPO Study)			Following 6 months of treatment, esomeprazole 20 mg was significantly more effective than pantoprazole 20 mg for maintaining endoscopic healing of erosive esophagitis (88.1% vs 76.6%; *P*<0.0001).
Scholten et al[42] Esomeprazole 40 mg DAILY vs pantoprazole 40 mg DAILY	DB, MC, PG, RCT Adult patients with GERD grade B and C (Los Angeles classification system) Patients excluded if they had peptic ulcers, Zollinger-Ellison syndrome, pyloric stenosis and esophageal and/or GI surgery	N=217 4 weeks	Primary: Relief of GERD-related symptoms Secondary: Relief rates of GERD-related symptoms, GSRS score, and time to first symptom relief	Primary: Both treatment groups reported similar relief of gastrointestinal symptoms (*P*>0.05). Secondary: At 4 weeks, the proportion of patients reporting no or mild heartburn was 99% with pantoprazole and 98% with esomeprazole. There were no significant differences in GSRS scores between the two treatment groups (*P*>0.05). Patients taking pantoprazole reported time to first symptom relief after a mean of 3.7 days compared to 5.9 days with esomeprazole (*P*=0.034).
Glatzel et al[43] Esomeprazole 40 mg DAILY for 4 weeks vs pantoprazole 40 mg DAILY for 4 weeks	DB, MC, PG, RCT Patients ≥18 years with endoscopically confirmed GERD grades A-D Patients excluded if they had a gastric hypersecretory condition, previous GI surgery, esophageal strictures, Barrett's esophagus, acute peptic ulcer or ulcer	N=561 6 weeks	Primary: Compare GERD symptom course by means of a validated reflux questionnaire (ReQuest®), number of symptom episodes, rate of relapse Secondary: Safety	Primary: Pantoprazole was shown to be as effective as esomeprazole based on mean ReQuest® score that evaluated GI symptoms. During the posttreatment period, the proportion of patients experiencing a symptomatic relapse (51% vs 61%; *P*=0.0216) and the number of symptom episodes (0.56 vs 0.74; *P*=0.0095) were significantly lower in patients on pantoprazole than on esomeprazole. Secondary: In general, both therapies were well tolerated and there was no significant difference in adverse events between the 2 treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	complications, pyloric stenosis or inflammatory bowel diseases			
EMANCIPATE Study[44] Esomeprazole 20 mg DAILY vs pantoprazole 20 mg DAILY	DB, MC, PG, RCT Patients ≥18 years with endoscopically confirmed GERD who received 4-8 weeks of pantoprazole 40 mg DAILY and were healed Patients excluded if they had Zollinger-Ellison syndrome or other gastric hypersecretory condition, pyloric stenosis, acute peptic ulcer and ulcer complications, endoscopically negative symptomatic GERD, esophageal strictures, Barrett's esophagus, or pregnant or nursing	N=1,303 6 months	Primary: Difference between combined endoscopic and symptomatic remission rates Secondary: Safety	Primary: Esomeprazole 20 mg DAILY and pantoprazole 20 mg DAILY were equally effective in maintaining patients in remission. In the intention-to-treat analysis, 85% of esomeprazole and 84% of pantoprazole patients remained in combined endoscopic and symptomatic remission at 6 months. Secondary: Both treatments were well tolerated and safe.
Sharma et al[45] Lansoprazole 30 mg DAILY	MA DB RCT trials in patients with	N=2,040 (6 trials) 4-8 weeks	Primary: Differences in pooled healing rates at 4 and 8	Primary: Pooled healing rates after 4 weeks were 77.7% for lansoprazole and 74.7% for omeprazole (absolute benefit increase 3.1%; 95% CI, –1.1 to 7.3) in the per protocol analysis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs omeprazole 20 mg DAILY	endoscopically diagnosed erosive esophagitis where healing rates had to be reported after 4 and/or 8 weeks		weeks per protocol and intention-to-treat data Secondary: Not reported	After 4 weeks, pooled healing rates were 72.7% for lansoprazole and 70.8% for omeprazole (absolute benefit increase 2.0%; 95% CI, –2.0 to 6.0) for the intention-to-treat analysis. After 8 weeks, pooled healing rates were 88.7% for lansoprazole and 87.0% for omeprazole (absolute benefit increase 1.7%; 95% CI, –1.5 to 5.0) in the per protocol analysis. After 8 weeks, pooled healing rates were 83.3% for lansoprazole and 81.8% for omeprazole (absolute benefit increase 1.5%; 95% CI, –1.9 to 4.9) in the intention-to-treat analysis. Lansoprazole and omeprazole healing rates were not statistically different. Secondary: Not reported
Richter et al[46] Lansoprazole 30 mg DAILY vs omeprazole 20 mg DAILY	DB, MC, RCT Adult patients with endoscopically documented erosive esophagitis Patients excluded if they had GI bleeding, history of gastric or esophageal surgery, esophageal motility disorders, esophageal stricture, or duodenal or gastric ulcers	N=3,510 8 weeks	Primary: Percentage of heartburn-free days and nights following 1-3 days and 1 week of treatment; and the frequency and severity of day- and nighttime heartburn Secondary: Not reported	Primary: The percentage of heartburn-free days was significantly higher with lansoprazole compared to omeprazole after 1-3 days of treatment and after 1 week of treatment (P<0.0001). The percentage of heartburn-free nights was significantly higher with lansoprazole compared to omeprazole after 1-3 days of treatment and after 1 week of treatment (P<0.0001). Average severity of heartburn symptoms was significantly less in patients taking lansoprazole compared to omeprazole. Significantly higher number of patients taking lansoprazole had recorded no heartburn compared to omeprazole at anytime during the first 14 days (P<0.001). At 8 weeks, the number of patients reporting no heartburn throughout the entire study was also significantly higher for lansoprazole (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Pilotto et al[47] Lansoprazole 30 mg DAILY vs omeprazole 20 mg DAILY vs pantoprazole 40 mg DAILY vs rabeprazole 20 mg DAILY Patients who were *H pylori* positive were treated with the PPI and 2 antibiotics (amoxicillin, clarithromycin or metronidazole) for 7 days.	OL, RCT Patients >65 years with endoscopically diagnosed esophagitis Patients excluded if history of Zollinger-Ellison syndrome, pyloric stenosis, previous surgery of the esophagus and/or GI tract, or GI malignancy	N=320 8 weeks	Primary: Healing of esophagitis, GI symptoms (eg, heart burn, acid regurgitation, epigastric pain), adverse events Secondary: Not reported	Primary: Intention-to-treat healing rates of esophagitis were 85.0% for lansoprazole, 75.0% for omeprazole, 90.0% for pantoprazole (*P*=0.02 vs omeprazole) and 88.8% for rabeprazole (*P*=0.04 vs omeprazole). Dividing patients according to the grades of esophagitis, omeprazole was significantly less effective than the 3 other PPIs in healing grade I esophagitis (healing rates 81.8% vs 100%, 100% and 100%, respectively; *P*=0.012). Healing rates were not significantly different for grades II (*P*=0.215) or III-IV (*P*=0.458) esophagitis. Pantoprazole and rabeprazole (100%) were more effective vs omeprazole (86.9%; *P*=0.0001) and lansoprazole (82.4%; *P*=0.0001) in decreasing heartburn. Omeprazole (100%), pantoprazole (92.2%), and rabeprazole (90.1%) were more effective vs lansoprazole (75.0%; *P*<0.05) in decreasing acid regurgitation. Omeprazole (95.0%), pantoprazole (95.2%), and rabeprazole (100%) were more effective vs lansoprazole (82.6%; *P*<0.05) in decreasing epigastric pain. All four PPIs were well tolerated and there was no significant difference in the prevalence of adverse events among the 4 treatment groups. Secondary: Not reported
Bardhan et al[48] Omeprazole 20 mg DAILY vs	OL, PG, RCT Adult patients with grade I GERD Patients were excluded if they had	N=327 8 weeks	Primary: Rate of symptom relief at weeks 2 and 4 and healing rates at week 4 and 8	Primary: At 2 and 4 weeks, the rate of symptom relief was similar for pantoprazole (70% and 77%) and omeprazole (79% and 84%; *P* value not reported). Healing rates at 4 weeks were comparable between pantoprazole (84%) and omeprazole (89%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pantoprazole 20 mg DAILY	grade II, III, IV GERD, GI bleeding, history of gastric or esophageal surgery, had Zollinger-Ellison syndrome, esophageal motility disorders, pyloric stenosis, esophageal stricture, or duodenal or gastric ulcers		Secondary: Not specified	Healing rates at 8 weeks were comparable between pantoprazole (90%) and omeprazole (95%; *P* value not reported). Secondary: Not reported
Delcher et al[49] Omeprazole 20 mg DAILY vs rabeprazole 20 mg DAILY vs rabeprazole 10 mg BID	DB, PG, RCT Adult patients with ulcerative or erosive GERD Patients excluded if they had grade I GERD, history of gastric or esophageal surgery, esophageal motility disorders, or pyloric stenosis	N=310 8 weeks	Primary: Healing rates Secondary: Improvement of GI symptoms, number of hours missed from normal daily activity, the use of antacids, and physical well-being	Primary: At 4 weeks, the rates of healing were comparable among rabeprazole 20 mg DAILY (94%), rabeprazole 10 mg BID (93%), and omeprazole (98%; *P* value not reported). At 4 weeks, the rates of healing were comparable among rabeprazole 20 mg DAILY (97%), rabeprazole 10 mg BID (98%), and omeprazole (100%; *P* value not reported). Secondary: At 4 and 8 weeks, improvements in GI symptoms were comparable among all treatment groups (*P* value not reported). Use of antacid tablets was comparable between all treatment groups (*P* value not reported). There were no significant differences between treatment groups in the General Well-Being Schedule (a quality-of-life measurement) or in a rating of overall physical well being.
Pace et al[50] Omeprazole 20 mg DAILY	DB, RCT Patients with grade I-III GERD	N=560 8 weeks	Primary: Healing rates Secondary: Time to first day	Primary: After 8 weeks, rates of healing for rabeprazole (97.9%) were equivalent to omeprazole (97.5%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs rabeprazole 20 mg DAILY			with satisfactory relief	Rabeprazole had a statistically faster time to satisfactory relief (2.8 days) compared to omeprazole (4.7 days; *P*=0.0045).
Peptic Ulcer Disease (PUD)				
Choi et al[52] Esomeprazole 40 mg BID vs omeprazole 20 mg BID vs pantoprazole 40 mg BID vs rabeprazole 20 mg BID PPI therapy was administered for 1 week along with amoxicillin 1 g BID and clarithromycin 500 mg BID.	PRO, RCT Patients who underwent upper endoscopy for various GI symptoms with *H pylori* infection documented by histologic examinations	N=576	Primary: *H pylori* eradication rates, side effects Secondary: Not reported	Primary: In the intention-to-treat analysis, no difference was found between the eradication rates for esomeprazole (70.3%), omeprazole (64.9%), pantoprazole (69.3%) and rabeprazole (69.3%; *P*=0.517). When eradication rates were analyzed according to whether patients had an ulcer or not on a per-protocol basis, no difference was found between the eradication rates for the four PPIs (*P*=0.610). Eradication rates for patients with peptic ulcer disease were 84.2% for esomeprazole, 80.0% for omeprazole, 78.9% for pantoprazole and 82.8% for rabeprazole (*P*=0.833). Eradication rates for patients with nonulcer dyspepsia were 87.5% for esomeprazole, 81.4% for omeprazole, 84.6% for pantoprazole and 73.1% for rabeprazole (*P*=0.412). Side effects were more common in the esomeprazole-based triple therapy group than in the other groups (*P*=0.038); however, the frequencies of individual symptoms were not significantly different among the four groups. Secondary: Not reported
Vergara et al[53] *H pylori* triple therapy with esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole	MA Randomized trials investigating *H pylori* triple therapy with a PPI with comparable antibiotic regimens differing only in the	14 trials 7-14 days	Primary: Direct comparison of eradication rates in the intention-to-treat population between PPIs	Primary: Pooled eradication rates with omeprazole (74.7%) were comparable to rates observed with lansoprazole (76%; OR, 0.91; 95% CI, 0.69 to 1.21). Pooled eradication rates with omeprazole (77.9%) were comparable to rates observed with rabeprazole (81.2%; OR, 0.81; 95% CI, 0.58 to 1.15). Pooled eradication rates with omeprazole (87.7%) were comparable to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	PPI utilized		Secondary: Not reported	rates observed with esomeprazole (89%; OR, 0.89; 95% CI, 0.58 to 1.35). Pooled eradication rates with lansoprazole (81%) were comparable to rates observed with rabeprazole (85.7%; OR, 0.77; 95% CI, 0.48 to 1.22). Secondary: Not reported
Ulmer et al[54] *H pylori* triple therapy with lansoprazole, omeprazole, or pantoprazole with two other antibiotics for 7 days	MA Clinical trials using PPI-based triple therapy for 7 days in *H pylori* infections	N=8,383 (79 trials) 7 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: Eradication rates for all therapies were 71.9%-83.9% in the intention-to-treat population and 78.5%-91.2% for the per-protocol analysis. Pooled data analysis indicated that lansoprazole-, omeprazole-, or pantoprazole-based therapies are comparable in *H pylori* eradication. Secondary: Not reported
Gisbert et al[55] Esomeprazole-based *H pylori* therapies vs omeprazole-based *H pylori* therapies	MA Randomized trials investigating the use of esomeprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	Number of trials analyzed not reported Treatment duration not reported	Primary: *H pylori* eradication rates for esomeprazole therapies Secondary: Comparison of eradication rates for esomeprazole vs omeprazole therapy	Primary: Dual therapy with esomeprazole and clarithromycin therapy resulted in eradication rates of 51%-54%. Mean eradication rates following triple therapy with esomeprazole, clarithromycin, and either amoxicillin or metronidazole were 82%-86%. Secondary: Mean eradication rates for esomeprazole-based therapies (85%) were comparable to omeprazole-based therapies (82%; OR, 1.19; 95% CI, 0.81 to 1.74).
Wang et al[56] Esomeprazole-based *H pylori* therapies vs	MA RCT investigating the use of esomeprazole-based *H pylori* therapies and other	N=2,159 (11 trials) 1 week (*H pylori* eradication)	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The mean *H pylori* eradication rates with esomeprazole-based therapies were comparable to that for other PPI-based regimens (86% vs 81%; OR, 1.38; 95% CI, 1.09 to 1.75). Subanalysis that included only studies comparing different doses of esomeprazole with omeprazole or pantoprazole did not reveal significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
omeprazole- and pantoprazole-based *H pylori* therapies	PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized			differences. No serious adverse events were reported. Secondary: Not reported
Hsu et al[57] Esomeprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week vs pantoprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week	PRO, RCT Patients ≥18 years old, infected with *H pylori*, with endoscopically proven peptic ulcer disease or gastritis	N=200 8 weeks (follow-up endoscopy)	Primary: *H pylori* eradication rates, adverse events, compliance Secondary: Ulcer healing	Primary: Intention-to-treat analysis demonstrated a significantly higher eradication rate for patients in the esomeprazole group than for the pantoprazole group (94% vs 82%; *P*=0.009). Both groups had similar frequencies of adverse events (15% vs 24%) and drug compliance (97% vs 96%). Secondary: Patients who had peptic ulcers diagnosed by initial endoscopy showed similar ulcer healing rates with esomeprazole (36/40) and pantoprazole (38/42) therapy.
Wu et al[58] Esomeprazole 40 mg DAILY, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week vs rabeprazole 20 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 1 week	PRO, RCT Patients with gastritis or peptic ulcer with *H pylori* infection	N=420 12-16 weeks (follow-up)	Primary: *H pylori* eradication rates, adverse events, compliance Secondary: Not reported	Primary: Intention-to-treat analysis revealed that the eradication rate was 89.4% in the esomeprazole group and 90.5% in the rabeprazole group (*P*=0.72). Compliance was reported in 100% and 99.5% of patients in the esomeprazole and rabeprazole groups, respectively (*P*=0.32). Adverse events were reported in 3.8% and 6.2% of patients in the esomeprazole and rabeprazole groups, respectively (*P*=0.27). Secondary: Not reported
Bazzoli et al[59] Lansoprazole-based *H pylori* therapies	MA Randomized trials investigating the use	N=1,354 16 trials	Primary: *H pylori* eradication rates for lansoprazole	Primary: Eradication rates for lansoprazole monotherapy (6-8 week duration) were comparable to dual therapy with lansoprazole (6-8 week duration) and amoxicillin (2-4 week duration; OR, 0.8; 95% CI, 0.3 to 1.9 for gastric

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs omeprazole-based *H pylori* therapies	of lansoprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized		therapies Secondary: Comparison of eradication rates for lansoprazole vs omeprazole therapy	ulcers; OR, 1.5; 95% CI, 0.4 to 5.7 for duodenal ulcers). Mean eradication rates for triple therapy with lansoprazole were significantly higher than observed with dual lansoprazole therapy (91.8% vs 57.1%; OR, 8.5; 95% CI, 2.9 to 24.5). Secondary: Mean eradication rates for lansoprazole-based therapies (80.6%) were comparable to omeprazole-based therapies (69.6%; OR, 0.9; 95% CI, 0.6 to 1.3).
Gisbert et al[60] Pantoprazole-based *H pylori* therapies vs lansoprazole- or omeprazole-based *H pylori* therapies	MA Randomized trials investigating the use of pantoprazole-based *H pylori* therapies and lansoprazole- or omeprazole-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	12 trials (Total N not reported) Treatment duration not reported	Primary: *H pylori* eradication rates for pantoprazole therapies Secondary: Comparison of eradication rates for pantoprazole vs other similar (same antibiotics and duration of use) PPI therapies, comparison of pantoprazole therapies to similar omeprazole and lansoprazole therapies	Primary: Fourteen-day therapy with pantoprazole 40 mg BID and clarithromycin 500 mg TID therapy resulted in a mean eradication rate of 60%. Mean eradication rates following 7-day therapies were as follows: pantoprazole-amoxicillin-clarithromycin 78%, pantoprazole-clarithromycin-nitroimidazole 84%, and pantoprazole-amoxicillin-nitroimidazole 74%. Secondary: Mean eradication rates for pantoprazole-based therapies (83%) with antibiotics were comparable to other PPI-based therapies (81%; OR, 1.0; 95% CI, 0.61 to 1.64). Mean eradication rates for pantoprazole-based therapies (83%) were comparable to omeprazole-based therapies (82%; OR, 0.91; 95% CI, 0.49 to 1.69). Mean eradication rates for pantoprazole-based therapies (78%) were comparable to those with lansoprazole-based therapies (75%; OR, 1.22; 95% CI, 0.68 to 2.17).
Gisbert et al[61] Rabeprazole-based *H pylori* therapies	MA Randomized trials investigating the use	12 trials (Total N not reported)	Primary: *H pylori* eradication rates for rabeprazole	Primary: Rabeprazole dual therapy with amoxicillin for 14 days resulted in a mean eradication rate of 73%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs lansoprazole- or omeprazole-based *H pylori* therapies	of rabeprazole-based *H pylori* therapies and lansoprazole- or omeprazole-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	Treatment duration not reported	therapies Secondary: Comparison of eradication rates for rabeprazole vs other similar (same antibiotics and duration of use) PPI therapies, comparison of rabeprazole therapies to similar omeprazole and lansoprazole therapies	Mean eradication rates for low-dose rabeprazole (20 mg/day) triple therapy with amoxicillin and clarithromycin for 7 days were 81% and 75% with high-dose rabeprazole (40 mg/day). Mean eradication rate for rabeprazole triple therapy with a nitroimidazole and clarithromycin for 7 days was 85%. Secondary: Mean eradication rate for rabeprazole-based therapies (79%) with antibiotics was comparable to other PPI-based therapies (77%; OR, 1.15; 95% CI, 0.93 to 1.42). Mean eradication rates for rabeprazole-based therapies (77%) were comparable to omeprazole-based therapies (77%; OR, 1.03; 95% CI, 0.81 to 1.32). Mean eradication rates for rabeprazole-based therapies (82%) were comparable to lansoprazole-based therapies (79%; OR, 1.17; 95% CI, 0.79 to 1.74).
Other				
Ramdani et al[62] Lansoprazole 30-120 mg/day or omeprazole 20-100 mg/day vs pantoprazole 40-200 mg/day All patients previously maintained on lansoprazole or omeprazole received pantoprazole for 7-10	OL, PRO Adult patients with Zollinger-Ellison syndrome maintained on omeprazole or lansoprazole Patients excluded if they had a history of gastric or esophageal surgery, GI malignancy, or a significant unstable disease	N=11 7-10 days	Primary: Median 24-hour intragastric pH and percentage of time at or below pH 3, 4, 5 and 6 Secondary: Basal acid output	Primary: Median 24-hour intragastric pH for pantoprazole (5.3) was comparable to the median pH for lansoprazole and omeprazole (4.6 for both agents; *P*=0.90). There were no significant differences in percentage of time at or below pH 3, 4, 5 and 6 between pantoprazole and lansoprazole or omeprazole (*P*>0.05). Secondary: Median basal acid output was similar between pantoprazole and lansoprazole or omeprazole (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days.				
Conrad et al[63] Immediate-release omeprazole suspension (two 40 mg dose on day 1 then 40 mg daily thereafter) vs cimetidine IV (300 mg bolus then 50 mg/hour thereafter)	DB, RCT Hospitalized patients >16 years old in the intensive care unit with an anticipated stay ≥72 hours with >1 additional risk for upper GI bleed Patients excluded for history of gastric surgery, allergy to cimetidine or omeprazole, active GI bleeding, significant risk of swallowing blood, enteral feeding required for the first 2 days of the trial, admission for upper GI surgery, known upper GI lesions that might bleed, the inability to take a suspension by nasogastric tube, or end-stage liver disease	N=359 14 days	Primary: Clinically significant upper GI bleed Secondary: Median gastric pH on each trial day, percentage of patients with median gastric pH of >4 on each trial day, and the percentage of patients with inadequate gastric pH control (2 consecutive pH measurements of ≤4)	Primary: Clinically significant upper GI bleeding was observed in 7 (3.9%) patients taking immediate-release omeprazole compared to 10 (5.5%) patients taking cimetidine (*P* value not reported). The upper bound of the one-sided 97.5% confidence interval for the difference in bleeding rates was 2.8%, less than the 5% prespecified "noninferiority" margin. Secondary: Median gastric pH was significantly higher in patients taking immediate-release omeprazole compared to cimetidine (median pH values not reported; *P*<0.001). A significantly higher percentage of patients on immediate-release omeprazole had median daily gastric pH >4 compared to patients on cimetidine (*P*≤0.01 on days 1-13, *P*=0.2 on day 14). A significantly higher percentage of patients on cimetidine had inadequate gastric pH control (58%) compared to immediate-release omeprazole (18.0%; *P*<0.001).
Katz et al[64] Immediate-release omeprazole suspension 40 mg for 7 days	OL, RCT, XO Non-Asian patients at least 18 years of age with a history of	N=54 Each treatment was for 7	Primary: Occurrence of nocturnal acid breakthrough (gastric pH <4 for	Primary: After 7 days of once-daily bedtime dosing, immediate-release omeprazole significantly reduced nocturnal acid breakthrough compared with esomeprazole and lansoprazole (61% vs 92% and 92%; *P*<0.001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs esomeprazole 40 mg for 7 days vs lansoprazole 30 mg for 7 days Following a 10-14 day washout between treatment periods, patients were crossed over to one of the alternative treatments.	GERD at least partially responsive to antacids or acid suppressants and had recurrent night-time symptoms for the previous 3 months, baseline gastric pH ≤2.5 prior to randomization Patients excluded for concurrent GI diseases other than GERD, a significant history of GI diseases in the past 5 years, any history of gastric surgery or any other significant unstable illness	days	more than 1 hour during the night-time from 22:00 to 06:00 hours) Secondary: Percentage of time gastric pH>4 and median gastric pH in cumulative 2-hour increments during the nighttime period and over 24 hours	Secondary: During the first half of the night, percentage of time with gastric pH >4 and median gastric pH were significantly higher after immediate-release omeprazole (52% and 4.34, respectively) compared to esomeprazole 30% and 2.37, respectively) or lansoprazole (12% and 1.51, respectively; *P*<0.001 for both comparisons). Over the 8-hour nighttime period, percentage of time with gastric pH >4 and median gastric pH were significantly higher after immediate-release omeprazole (53% and 4.04, respectively) than lansoprazole (34% and 2.09, respectively; *P*<0.001 for both comparisons) but comparable to esomeprazole (55% and 4.85, respectively). The percentage of time with gastric pH >4 for the 24-hour period was 44% with immediate-release omeprazole vs 59% with esomeprazole (*P*<0.001) and 28% with lansoprazole (*P*<0.001 for both comparisons).
Castell et al[65] Immediate-release omeprazole suspension dosed 40 mg daily for 1 week, then 20 or 40 mg BID daily for 1 day vs pantoprazole 40 mg daily for 1 week, then 40 mg BID daily for 1 day Study participants	OL, RCT, XO Adult patients 18-65 years old with GERD and recurrent nighttime symptoms for the previous 3 months Patients excluded if they had current gastrointestinal disease other than GERD, history of gastric surgery,	N=36 16 days	Primary: Control of nocturnal gastric acidity measured by the following: percentage of time with gastric pH >4, median gastric pH, and nocturnal acid breakthrough Secondary: Not reported	Primary: Median percentage of time with gastric pH >4 was significantly higher with immediate-release omeprazole (54.7%) compared to pantoprazole (26.5%; *P*<0.001). Median gastric pH was significantly higher with immediate-release omeprazole (4.7) compared to pantoprazole (2.0; *P*<0.001). Significantly less nocturnal acid breakthrough was observed with immediate-release omeprazole (53.1%) compared to pantoprazole (78.1%; *P*=0.005). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
underwent 8 days of treatment followed by a 10-14 day washout period. Afterwards participants underwent an additional 8 days of treatment on the other agent.	other significant, unstable disease or use of any gastric antisecretory drugs 7 days prior to the trial			
Regula et al[66] Omeprazole 20 mg DAILY vs pantoprazole 20 mg DAILY vs pantoprazole 40 mg DAILY	DB, MC, PG, RCT, Rheumatic patients >55 years on continual NSAIDs and with at least 1 more recognized risk factor that contributes to the development of GI injury Patients excluded if they had Zollinger-Ellison syndrome, esophageal structures, previous surgery of the GI tract, current peptic ulcer or peptic ulcer complication	N=595 6 months	Primary: Therapeutic failure (peptic ulcer, more than 10 erosions or petechiae in the stomach or duodenum, reflux esophagitis, or study discontinuation due to GI symptoms or an adverse event) and lack of endoscopic failure at 6 months, adverse events Secondary: Primary end points at 3 months	Primary: After 6 months, the probabilities to remain in remission were 90% pantoprazole 20 mg DAILY, 93% pantoprazole 40 mg DAILY, and 89% omeprazole 20 mg DAILY for lack of therapeutic failure (*P* values not reported). After 6 months, the probabilities to remain in remission were 91% pantoprazole 20 mg DAILY, 95% pantoprazole 40 mg DAILY and 93% omeprazole 20 mg DAILY for lack of endoscopic failure (*P* values not reported. During the study, a similar proportion of patients reported adverse events in each treatment group (29% of patients receiving pantoprazole 20 mg DAILY; 37% of patients receiving pantoprazole 40 mg DAILY; 33% of patients receiving omeprazole 20 mg DAILY; *P* values not reported). Secondary: After 3 months, the probabilities to remain in remission were 94% pantoprazole 20 mg DAILY, 97% pantoprazole 40 mg DAILY, and 94% omeprazole 20 mg DAILY for lack of therapeutic failure (*P* values not reported). After 3 months, the probabilities to remain in remission were 96% pantoprazole 20 mg DAILY, 99% pantoprazole 40 mg DAILY and 96% omeprazole 20 mg DAILY for lack of endoscopic failure (*P* values not reported.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, PPI=proton-pump inhibitor, PRN=as needed, TID=three times a day

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, XO=crossover
Miscellaneous abbreviations: GERD=gastroesophageal reflux disease, GI=gastrointestinal, GSRS=GI symptom rating scale, *H pylori=Helicobacter pylori*, NSAIDS=nonsteroidal anti-inflammatory drugs, PUD=peptic ulcer disease

Special Populations

Table 5. Special Populations[4-16]

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
Esomeprazole	No dosage adjustment required in the elderly. Approved for use in children ages 1-17 years.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate liver impairment. Do not exceed a dose of 20 mg in patients with severe liver impairment.	B	Unknown	
Lansoprazole	No dosage adjustment required in the elderly. Approved for use in children ages 1-17 years.	No dosage adjustment required.	Dosage adjustment for patients with severe liver disease should be considered.	B	Unknown	Oral disintegrating tablet contains phenylalanine.
Omeprazole	No dosage adjustment required in the elderly. Approved for use in children ages 1-16 years (Prilosec).	No dosage adjustment required.	Dosage reduction should be considered, particularly for maintenance of healing of erosive esophagitis.	C	Yes (% unknown)	Dosage reduction for Asian patients should be considered, particularly for maintenance of healing of erosive esophagitis.
Omeprazole and sodium bicarbonate	No dosage adjustment required in the elderly. Not studied in the pediatric population.	No dosage adjustment required.	Dosage adjustment should be considered, particularly for maintenance of healing of erosive esophagitis.	C	Yes (% unknown)	Dosage adjustment for Asian patients should be considered, particularly for maintenance of healing of erosive esophagitis. Caution advised for

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
						patients on a sodium-restricted diet.
Pantoprazole	No dosage adjustment required in the elderly. Not studied in the pediatric population.	No dosage adjustment required.	No dosage adjustment required; however, doses higher than 40 mg/day have not been studied in hepatically-impaired patients.	B	Unknown	
Rabeprazole	No dosage adjustment required in the elderly. Approved for use in children ≥12 years.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate liver impairment. Caution advised for patients with severe liver impairment.	B	Unknown	

Adverse Drug Events

Table 6 summarizes the most common adverse events associated with oral administration of the proton-pump inhibitors (PPIs). The PPIs are generally well tolerated with abdominal pain, diarrhea, flatulence, headache, nausea and vomiting reported as the most frequent side effects. Long-term use of PPIs for 5 or more years has been associated with an increase in hip fractures.[70] When administered for 7 or more years, PPIs were associated with a significantly increased risk of an osteoporosis-related fracture. At this time, there is inadequate evidence to mandate bone density studies and calcium supplementation in patients receiving chronic PPI therapy.[18] Additional studies are needed to determine the value of osteoprotective medications for patients receiving long-term therapy with PPIs.[70]

Table 6. Adverse Drug Events[4-16]

Adverse Event(s)	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Central Nervous System					
Anxiety	-	-	-	≥1	-
Asthenia	-	-	1.1-1.3	≥1	-
Dizziness	-	-	1.5	≥1	-
Fatigue	-	✔	-	-	-
Headache	1.9-8.1	✔	2.9-6.9	2-9	5.4-9.9
Insomnia	-	-	-	≤1	-
Somnolence	1.9	-	-	-	-
Dermatological					
Erythema	✔	-	-	-	-

Adverse Event(s)	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
multiforme					
Rash	-	-	1.5	≤2	-
Stevens-Johnson syndrome	✔	-	-	✔	✔
Toxic epidermal necrolysis	✔	-	-	✔	-
Endocrine and Metabolic					
Liver function abnormalities	-	-	-	2	-
Gastrointestinal					
Abdominal pain	2.7-3.8	1.8-2.1	2.4-5.4	1-4	3.6
Acid regurgitation	-	-	1.9	-	-
Atropic gastritis	-	-	-	✔	-
Constipation	✔	1.0	1.1-1.5	≥1	2
Diarrhea	1-10	<8.0	3.0-3.7	2-6	4.5
Dry mouth	✔	-	-	-	-
Dyspepsia	-	-	-	≥1	-
Flatulence	✔	-	2.7	2-4	3
Gastroenteritis	-	-	-	≥1	-
Hepatotoxicity	-	-	✔	-	-
Nausea	1-10	≤3.7	2.2-4.0	2	1.8-4.5
Pancreatitis	✔	-	✔	-	-
Vomiting	-	-	1.5-3.2	2	3.6
Genitourinary					
Interstitial nephritis	-	-	✔	-	-
Urinary tract infection	-	-	-	≥1	-
Hematologic					
Thrombocytopenia	-	-	-	✔	-
Laboratory Test Abnormalities					
Elevated serum glutamic pyruvic transaminase	-	-	-	≥1	-
Musculoskeletal					
Arthralgia	-	-	-	≥1	-
Back pain	-	-	1.1	≥1	-
Hip fracture	✔	✔	✔	✔	✔
Pain	-	-	-	-	3
Rhabdomyolysis	✔	✔	✔	✔	✔
Respiratory					
Bronchitis	-	-	-	≥1	-
Cough	-	-	1.1	≥1	-
Dypsnea	-	-	-	≥1	-
Pharyngitis	-	-	-	≥1	3
Rhinitis	-	-	-	≥1	-
Sinusitis	-	-	-	≥1	-
Upper respiratory tract infection	-	-	1.9	≥1	-
Other					
Fever	-	-	✔	-	-
Flu-like syndrome	-	-	-	≥1	-

Adverse Event(s)	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Infection	-	-	-	-	2

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications / Precautions

Proton-pump inhibitors (PPIs) are contraindicated in patients with known hypersensitivity to substituted benzimidazoles.[4-16] Symptomatic response to PPIs does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in patients receiving long-term pantoprazole and omeprazole therapy. Generally, daily treatment with any acid-suppressing medication over a long period of time (eg, longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B12).

Each Zegerid® capsule contains 1,100 mg (13 mEq) of sodium bicarbonate.[16] The total content of sodium in each capsule is 304 mg. Each packet of Zegerid® powder for oral suspension contains 1,680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+). The sodium content of Zegerid® products should be taken into consideration when administering to patients on a sodium-restricted diet. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

Drug Interactions

Table 7. Drug Interactions[4-16]

Generic Name	Interacting Medication or Disease	Potential Result
Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Azole antifungals	Proton-pump inhibitors (PPIs) may reduce the bioavailability of certain azole antifungals, reducing plasma levels and antifungal activity. Concurrent use should be avoided. If concurrent use is necessary, administer the oral azole antifungal with an acidic beverage.
Esomeprazole, lansoprazole	Clarithromycin	The metabolism of certain PPIs may be inhibited by clarithromycin causing increases in plasma levels of the PPIs. Patients should be monitored for an increase in adverse reactions during concurrent administration.
Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Protease inhibitors	PPIs may reduce the dissolution of certain protease inhibitors, reducing gastrointestinal absorption and antiviral activity. Saquinavir plasma levels may increase. Dose adjustment of some protease inhibitors may be required with concurrent administration. The use of PPIs with atazanavir is not recommended.
Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Warfarin	Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in International Normalized Ratio and prothrombin time.
Omeprazole	Cilostazol	Omeprazole may inhibit the metabolism of cilostazol. A dose decrease of cilostazol to 50 mg twice daily may be required during concurrent administration with omeprazole.
Omeprazole	Tacrolimus	Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Dosage and Administration

To maximize efficacy, Proton-pump inhibitors (PPIs) should be taken before the first meal of the day.[3]

Table 8. Dosing and Administration[4-16]

Generic Name	Adult Dose	Pediatric Dose	Availability
Esomeprazole	Erosive esophagitis: Capsule, suspension, vial: treatment, 20-40 mg DAILY for 4-8 weeks (IV formulation is indicated for up to 10 days); for patients who do not heal after 4-8 weeks, an additional 4-8 weeks of treatment may be considered; maintenance, 20 mg DAILY; controlled trials do not extend beyond 6 months GERD, symptomatic: Capsule, suspension: 20 mg DAILY for 4 weeks; an additional 4 weeks may be considered if symptoms do not completely resolve *H pylori* eradication: Capsule, suspension: 40 mg DAILY for 10 days (as triple therapy with amoxicillin 1,000 mg BID plus clarithromycin 500 mg BID for 10 days) Pathological hypersecretory conditions: Capsule, suspension: 40 mg BID (doses up to 240 mg daily have been administered) Risk reduction of NSAID-associated gastric ulcer: Capsule, suspension: 20 or 40 mg DAILY for up to 6 months; controlled trials do not extend beyond 6 months Take at least 1 hour before meals.	Erosive esophagitis, treatment 1-11 years old: Capsule, suspension: <20 kg give 10 mg DAILY for 8 weeks, ≥20 kg give 10-20 mg DAILY for 8 weeks GERD, symptomatic 1-11 years old: Capsule, suspension: 10 mg DAILY for up to 8 weeks GERD, symptomatic 12-17 years old: Capsule, suspension: 20 mg or 40 mg DAILY for up to 8 weeks Note: take at least 1 hour before meals.	Capsule, delayed-release (for oral or nasogastric tube): 20 mg 40 mg Suspension, delayed-release (for oral or nasogastric or gastric tube): 10 mg 20 mg 40 mg Vial: 20 mg 40 mg
Lansoprazole	Duodenal ulcer: Capsule, suspension, tablet: treatment, 15 mg DAILY for 4 weeks; maintenance, 15 mg DAILY Erosive esophagitis: Capsule, suspension, tablet, vial: treatment, 30 mg DAILY for up to 8 weeks (IV formulation is	Erosive esophagitis, treatment and GERD, symptomatic 1-11 years old: Capsule, suspension, tablet: ≤30 kg give15 mg DAILY for up to 12 weeks; >30 kg give 30 mg DAILY for up to 12 weeks; dose	Capsule, delayed-release (oral or nasogastric tube): 15 mg 30 mg Suspension, delayed-release (oral): 15 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	indicated for use up to 7 days); for patients who do not heal after 8 weeks or have a recurrence, an additional 8 weeks of treatment may be considered; maintenance, 15 mg DAILY Gastric ulcer, treatment: Capsule, suspension, tablet: 30 mg DAILY up to 8 weeks GERD, symptomatic: Capsule, suspension, tablet: 15 mg DAILY for up to 8 weeks *H pylori* eradication: Capsule, suspension, tablet: 30 mg BID for 10 or 14 days (as triple therapy with amoxicillin 1,000 mg BID plus clarithromycin 500 mg BID for 10 or 14 days) or 30 mg TID for 14 days (as dual therapy with amoxicillin 1,000 mg BID for 14 days) NSAID-associated gastric ulcer, treatment: Capsule, suspension, tablet: 30 mg DAILY for 8 weeks NSAID-associated gastric ulcer, risk reduction: Capsule, suspension, tablet: 15 mg DAILY up to 12 weeks Pathological hypersecretory conditions: Capsule, suspension, tablet: 60 mg DAILY up to 90 mg BID Take before eating.	was increased up to 30 mg BID in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic GERD, symptomatic 12-17 years old: Capsule, suspension, tablet: 15-30 mg DAILY for up to 8 weeks Note: take before eating.	30 mg Tablet, orally disintegrating, delayed-release (oral or nasogastric tube): 15 mg 30 mg Vial: 30 mg
Omeprazole	Duodenal ulcer disease, treatment: Capsule, suspension: 20 mg DAILY for 4-8 weeks Erosive esophagitis: Capsule, suspension: treatment, 20 mg DAILY for 4-8 weeks; maintenance: 20 mg DAILY Gastric ulcer, treatment: Capsule, suspension: 40 mg	Erosive esophagitis, maintenance and GERD, symptomatic 1-16 years old: Capsule, suspension: 5-10 kg give 5 mg per day, 10-20 kg give 10 mg per day, ≥20 kg give 20 mg per day Take before eating.	Capsule, delayed-release (oral): 10 mg 20 mg 40 mg Suspension, delayed-release (oral or nasogastric or gastric tube): 2.5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	DAILY for 4-8 weeks GERD, symptomatic: Capsule, suspension: 20 mg DAILY for 4 weeks *H pylori* eradication: Capsule, suspension: 20 mg BID for 10 days (as triple therapy with amoxicillin 1,000 mg BID plus clarithromycin 500 mg BID for 10 days) with an additional 18 days of omeprazole 20 mg DAILY for patients with an ulcer present at the time of initiation of therapy or 40 mg DAILY for 14 days (in as dual therapy with clarithromycin 500 mg TID for 14 days) with an additional 14 days of omeprazole 20 mg DAILY for patients with an ulcer present at the time of initiation of therapy Pathological hypersecretory conditions: Capsule, suspension: 60 mg DAILY up to 120 mg TID Take before eating.		10 mg
Omeprazole magnesium	Heartburn: Tablet: 20 mg DAILY for 14 days; an additional 14 day treatment course may be repeated every 4 months Take before eating.	Safety and efficacy in children have not been established.	Tablet, delayed-release (oral): 20 mg
Omeprazole and sodium bicarbonate	Duodenal ulcer, treatment: Capsule, suspension: 20 mg DAILY for 4-8 weeks Gastric ulcer, treatment: Capsule, suspension: 40 mg DAILY for 4-8 weeks Erosive esophagitis: Capsule, suspension: treatment, 20 mg DAILY for 4-8 weeks; maintenance, 20 mg DAILY GERD, symptomatic: Capsule, suspension: 20 mg DAILY for 4 weeks	Safety and efficacy in children have not been established.	Capsule (oral): 20 mg 40 mg Suspension (oral or nasogastric or orogastric tube): 20 mg 40 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Upper GI hemorrhage, risk reduction: Suspension: initial, 40 mg followed by 40 mg 6-8 hours later and 40 mg thereafter for 14 days Take on an empty stomach at least 1 hour before a meal. Two capsules or packets of 20 mg should not be substituted for one capsule or packet of 40 mg since they are not equivalent.		
Pantoprazole	Erosive esophagitis: Suspension, tablet: treatment, 40 mg DAILY for up to 8 weeks; for patients who do not heal after 8 weeks, an additional 8 weeks of treatment may be considered; maintenance: 40 mg DAILY GERD associated with history of erosive esophagitis: Vial: 40 mg DAILY for 7-10 days Pathological hypersecretory conditions: Suspension, tablet: 40 mg BID up to 240 mg daily; vial: 80 mg BID up to 240 mg daily for up to 6 days May be taken with or without food.	Safety and efficacy in children have not been established	Suspension, delayed-release (oral or nasogastric tube): 40 mg Tablet, delayed-release: 20 mg 40 mg Vial: 40 mg
Rabeprazole	Duodenal ulcer disease, treatment: Tablet: 20 mg DAILY for 4 weeks Erosive esophagitis: Tablet: treatment, 20 mg DAILY for 4-8 weeks; for patients who do not heal after 8 weeks, an additional 8 weeks of treatment may be considered; maintenance: 20 mg DAILY GERD, symptomatic: Tablet: 20 mg DAILY for 4 weeks; if symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered *H pylori* eradication: Tablet: 20 mg BID for 7 days (as triple therapy with amoxicillin	GERD, short-term treatment ≥12 years: Tablet: 20 mg DAILY for up to 8 weeks	Tablet, delayed-release: 20 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	1,000 mg BID plus clarithromycin 500 mg BID for 7 days) Pathological hypersecretory conditions: Tablet: 60 mg DAILY up to 60 mg BID May be taken with or without food.		

BID=twice daily, GERD=gastroesophageal reflux disease, IV=intravenous, NSAID=nonsteroidal anti-inflammatory drug

Other Key Facts

Clinical Guidelines

Table 9. Clinical Guidelines Using the Single Entity Proton-pump Inhibitors

Clinical Guideline	Recommendations
American College of Gastroenterology: **Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease (GERD) (2005)**[17]	• Antacids and over-the-counter (OTC) acid suppressants are options for patient-directed therapy for heartburn. Patients should be evaluated if symptoms persist and they require continuous therapy. • Acid suppression is the mainstay of GERD therapy and proton-pump inhibitors (PPIs) provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients.
American Gastroenterological Association: **Medical Position Statement on the Management of GERD (2008)**[18]	• Antisecretory drugs are recommended for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief). In these conditions, PPIs are more effective than histamine H_2-receptor antagonists (H_2RAs), which are more effective than placebo. • Twice-daily PPI therapy is recommended for patients who had an inadequate symptom response to once-daily PPI therapy. There is no evidence of improved efficacy by adding a nocturnal dose of an H_2RA to twice-daily PPI therapy. • A short course or as needed use of antisecretory drugs is recommended in patients with a symptomatic esophageal syndrome without esophagitis when symptom control is the primary objective. For a short course of therapy, PPIs are more effective than H_2RAs, which are more effective than placebo. • Circumstances in which one antisecretory drug might be preferable to another primarily relate to side effects or onset of effect. The most common side effects of PPIs are abdominal pain, constipation, diarrhea, and headache which can usually be circumvented by switching among alternative PPIs or lowering the PPI dose. Medications taken in response to symptoms should be rapidly acting. The most rapidly acting agents are antacids, the efficacy of which can be sustained by combining them with a PPI or H_2RA. • Long-term use of PPIs is recommended for the treatment of patients with esophagitis once they have proven clinically effective. Long-term therapy should be titrated down to the lowest effective dose based on symptom control. On-demand therapy is a reasonable strategy in patients with an esophageal GERD syndrome without esophagitis, where symptom control is the primary objective.

Clinical Guideline	Recommendations
	• Less than daily dosing of PPI therapy as maintenance therapy is not recommended in patients with an esophageal syndrome who previously had erosive esophagitis.
American College of Gastroenterology: **Guidelines for the Management of Dyspepsia (2005)**[19]	• Empiric trial with a PPI for 4-8 weeks as an initial therapy option is recommended in dyspeptic patients ≤55 years old without alarm features (eg, bleeding, dysphagia, family history of gastrointestinal cancer, weight loss) and where *H pylori* prevalence is low (<10%). • If initial acid suppression fails after 2-4 weeks, it is reasonable to consider changing drug class or dosing. In patients who respond to initial therapy, stop treatment after 4-8 weeks; if symptoms recur, another course of the same treatment is justified. • In populations with a moderate-to-high prevalence of *H pylori* infection (≥10%), test and treat for *H pylori* and give a trial of acid suppression if eradication is successful but symptoms do not resolve. • Dyspeptic patients >55 years old or who have alarm features should undergo prompt esophagogastroduodenoscopy to rule out peptic ulcer disease, esophagogastric malignancy and other upper gastrointestinal diseases.
American Gastroenterological Association: **Medical Position Statement: Evaluation of Dyspepsia (2005)**[20]	• Patients with dyspepsia (without GERD or nonsteroidal anti-inflammatory drugs [NSAIDS]) who are ≤55 years old and do not have any alarm features should receive *H pylori* testing and treatment of positive cases followed by acid suppression if symptoms remain. PPIs are the drug class of choice for acid suppression. • Patients who are *H pylori* negative should be prescribed an empirical trial of acid suppression with a PPI for 4-8 weeks. • Empirical PPI therapy is the most cost-effective approach in populations with a low prevalence of *H pylori* (≤10%). • Patients with dyspepsia who are >55 years old or who have alarm features should have an esophagogastroduodenoscopy with biopsy for *H pylori*. Treatment should be targeted at the underlying diagnosis.
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection (2007)**[21]	• In the United States (US), the recommended primary therapies for *H pylori* infection include: a PPI, clarithromycin, and amoxicillin or metronidazole (clarithromycin-based triple therapy) for 14 days for eradication rates of 70%-85% or a PPI or histamine-2 receptor antagonist, bismuth, metronidazole, and tetracycline (bismuth-based quadruple therapy) for 10-14 days for eradication rates of 75%-90%. • The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole and rabeprazole) in clarithromycin-based triple regimens is more effective than once daily dosing. • Sequential therapy consisting of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days may provide an alternative to clarithromycin-based triple or bismuth-based quadruple therapy but requires validation within the United States before it can be recommended as a first-line therapy. • In patients with persistent *H pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient. Bismuth-based quadruple therapy for 7-14 days is an accepted salvage therapy. Levofloxacin-based triple therapy for 10 days is another option for patients with persistent infection but this regimen requires validation in the United States.

Clinical Guideline	Recommendations
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H pylori* Infection–The Maastricht III Consensus Report (2007)**[22]	• Recommended first-line treatment is a PPI, clarithromycin and amoxicillin or metronidazole in populations with less than 15%-20% clarithromycin resistance. In populations with less than 40% metronidazole resistance a regimen containing a PPI, clarithromycin and metronidazole is preferable. A 14-day treatment regimen is 12% more effective than a 7-day regimen. A 7-day treatment regimen may be acceptable where local studies show that it is effective. • Bismuth-based quadruple therapies (10 or 14 days) are alternative first-choice treatments. • Bismuth-based quadruple therapies remain the best second-choice treatment. If not available, a PPI, amoxicillin or tetracycline and metronidazole are recommended.
American College of Cardiology Foundation (ACCF)/ACG/American Heart Association: **2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use (2008)**[23]	• PPIs are the preferred agents for the therapy and prophylaxis of aspirin- and NSAID-associated gastrointestinal injury.

Conclusions

Proton-pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available.[1] All of the PPIs are Food and Drug Administration (FDA) approved for the treatment and maintenance of Gastroesophageal Reflux Disease (GERD) and the treatment of pathological hypersecretory conditions.[4-16] With the exception of pantoprazole, all of the PPIs are approved for the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence. Pantoprazole is the only PPI that is not FDA approved for use in children. All PPIs are available in delayed-release oral formulations and can be dosed once daily. With the exception of rabeprazole, all of the PPIs are available in an oral suspension. Omeprazole is also available as an immediate-release capsule and an over-the-counter (OTC) formulation. Esomeprazole, lansoprazole, and pantoprazole are available in intravenous formulations for short-term use in patients unable to take medications by mouth. Omeprazole and pantoprazole are available generically.

Current medical evidence has demonstrated that PPI therapy is highly effective in treating, providing symptomatic relief, and preventing relapse in gastric acid disorders such as erosive esophagitis and symptomatic GERD.[25-51] In meta-analyses and direct comparator trials lansoprazole, omeprazole, pantoprazole, and rabeprazole all demonstrated comparable healing rates, maintenance of healing, or symptomatic relief of GERD.[25,27,29,31,32,35,37,40,41] A few studies reported statistically faster and greater symptomatic relief with lansoprazole compared to omeprazole; however, the significance of these differences in clinical practice is not known.[46] There is evidence through meta-analyses and several clinical trials that esomeprazole provides higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole and pantoprazole.[25,27,29,31,32,35,37,40,41] Subgroup analyses in a few trials noted better healing rates with esomeprazole in patients with more severe disease.[38,40] Close analysis of all of these studies show that the overall differences were generally small. Though the results are statistically significant, the clinical significance of these differences is not known. The results of these trials have not been replicated consistently in other trials, particularly in trials with lansoprazole and pantoprazole.[28,30,36,39,42,44] It should be noted that most trials that compared esomeprazole to omeprazole employed doses of 40 mg for esomeprazole and 20 mg for omeprazole.[25,27,35,37] Since esomeprazole is a stereoisomer of omeprazole,

comparing 40 mg of esomeprazole to 20 mg of omeprazole is comparable to evaluating a double dose of omeprazole to a single dose of omeprazole. A 2007 Cochrane review concluded that there was no major difference in efficacy among the currently available PPIs for the short-term management of reflux esophagitis when administered in equivalent dosages.[51] Currently, there are no trials directly comparing the different omeprazole formulations to one another.

Clinical studies have demonstrated that PPIs are also highly effective in the treatment of peptic ulcer disease caused by chronic nonsteroidal anti-inflammatory drug (NSAID) therapy or *H pylori* infection when coupled with antibiotics.[52-66] Meta-analyses and head-to-head trials comparing PPIs to each other have shown comparable rates of eradication when administered at comparable doses and paired with comparable antibiotic regimens. One small trial reported higher eradication rates for patients treated with esomeprazole than pantoprazole.[57] A few studies have noted higher eradication rates of *H pylori* in patients who were poor metabolizers of PPIs.[3,24] Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.

Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy.[17-20,23] Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H pylori*.[21,22] None of the treatment guidelines recommend one PPI over another or one formulation of a PPI over another.[17-23]

Comparative data regarding the PPIs has not demonstrated distinct, clinically significant differences regarding safety and tolerability. Overall, no one PPI offers a significant clinical advantage over another. Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in this class and offer no significant clinical advantage over other alternatives in general use.

Recommendations

In recognition of the well-established role of the single entity proton-pump inhibitors (PPIs) for the treatment of gastrointestinal disorders, their extended track record of efficacy and safety and comparable safety and efficacy profiles of all agents in the class, it is recommended that no changes be made to the current approval criteria.

Nexium powder for suspension, Prevacid Solutabs (for patients ≥ 12 years old), Protonix packet, Zegerid powder for suspension (for patients ≥ 16 years old) require prior authorization with the following approval criteria:

- The patient has a requirement for an oral liquid dosage form.

Other non-preferred medications require prior authorization with the following approval criteria:

- The member has had a documented side effect, allergy, or treatment failure to Prilosec OTC tablets, Protonix tablets, AND Prevacid capsules.

A quantity limit of one dose per day applies to all drugs within this category. If twice daily dosing is desired, the following approval criteria must be met:

- Gastroesophageal Reflux Disease (GERD) – If member has had an adequate trial (e.g. 8 weeks) of standard once daily dosing for GERD, twice daily dosing may be approved.
- Zollinger-Ellison (ZE) syndrome – Up to triple dose PPI may be approved.
- Hypersecretory conditions (endocrine adenomas or systemic mastocytosis) – Double dose PPI may be approved.
- Erosive Esophagitis, Esophageal stricture, Barrett's esophagitis (complicated GERD) – Double dose PPI may be approved.
- Treatment of ulcers caused by H. Pylori – Double dose PPI may be approved for up to 2 weeks.
- Laryngopharyngeal reflux – Double dose PPI may be approved.

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